NETWise
A Podcast About Neuroendocrine Cancer

Episode 46:
Neuroendocrine carcinoma 101
Transcript

Multiple times a week, Susan Meckler-Plummer gets on a call to talk to people at one of the most challenging moments of their lives.

> ***Meckler Plummer:*** *They are confused. Their worlds have been turned upside down.*

These people are from all over the world. They are different ages, genders, races, and backgrounds. But they have one thing in common: they have been diagnosed with neuroendocrine carcinoma. This is an uncommon and aggressive form of cancer with no known cure.

> ***Meckler Plummer:*** *When people get diagnosed, when they see their oncologist and they get this, this awful diagnosis, they tend to shut down. They are told a few things. They probably aren't absorbing it at all.*

Susan runs an online support group for patients with neuroendocrine carcinoma. When a new person joins the group, she sets up a time to talk with them one-on-one.

> ***Meckler Plummer:*** *And so we literally start from the beginning, understanding pathology, understanding what that means, what that looks like, and just take it from there.*

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You're listening to NETWise. I'm Jessica Thomas, Director of Patient Education at NETRF. In each episode of this podcast, we share expert information and patient perspectives to help neuroendocrine cancer patients and caregivers navigate their journeys.

Many kinds of neuroendocrine cancer are slow-growing, and can be treated like a chronic disease. But some kinds of neuroendocrine cancer are highly aggressive. These are neuroendocrine carcinomas.

In this episode of NETWise, we're going to do the same thing Susan does when she talks with newly diagnosed patients: we'll walk through the essential information about neuroendocrine carcinoma, from understanding what this cancer is, to the diagnostic process, to treatment options.

If you or a loved one has recently been diagnosed with this disease, this is the place to begin.

Welcome.

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Long before someone talks with Susan Meckler-Plummer about their neuroendocrine carcinoma diagnosis, something very subtle happens inside their body: a cell develops a glitch.

Dr. Carl Gay is a thoracic medical oncologist and research scientist at the University of Texas MD Anderson Cancer Center.

> ***Gay:*** *You know, in adult humans, most of our cells have done most of the growing and dividing that their plan for the entire duration of their lives. And there are these checks and balances that keep them in that state. And invariably one or more of those checkpoints goes awry, and allows cells to grow and divide often without any checks and balances whatsoever.*

This results in the growth of something called a neoplasm, or tumor. This is an abnormal growth of cells. It can be either benign or malignant, depending on how the cells behave.

Dr. Aman Chauhan is a medical oncologist at the Sylvester Comprehensive Cancer Center at the University of Miami, where he leads the neuroendocrine cancer program.

> ***Chauhan:*** *So a benign neoplasm would imply that it's abnormal growth, but it's still restricted to where it*

started. But there are growths that during its development acquire mutations. These are genetic changes that give them superpower to break out and invade another organ. Those are called malignant growths, otherwise also known as cancers.

Cancer is a disease characterized by uncontrolled growth and spread of cancer cells. This spread is known as metastasis.

Dr. Renuka Iyer is a medical oncologist at Roswell Park Comprehensive Cancer Center in Buffalo, New York.

Iyer: *Cancer knows how to grow uncontrolled and spread and travel and move from one place to the other. Which is what makes it undesirable, and, you know, deadly if it can travel and spread to other parts of the body.*

With neuroendocrine cancer, the cell that goes haywire is a neuroendocrine cell. These are a unique kind of cell, present throughout the body.

Iyer: *And these are, as the name suggests, "neuro" means brain and "endocrine" means hormone. So these are the brain-hormone cells or the signaling cells that are taking some impulses or chemical signals from the brain and turning them into a local hormonal response or message to the other cells, telling them what to do.*

When one of these cells becomes cancerous, it can multiply and form a tumor, just like any other kind of cancer. It can also metastasize to other parts of the body.

While neuroendocrine cancers share these essential qualities with other cancers, there are a few things that set them apart.

The first distinguishing quality of neuroendocrine cancers is that they are uncommon. It's estimated that neuroendocrine

cancer affects only about 6 in every hundred-thousand people worldwide.

The second thing that sets neuroendocrine cancers apart from other cancers is that these tumors sometimes release excess hormones into the body. These are called "functional" neoplasms, and they can cause a variety of unique symptoms.

The final thing that sets neuroendocrine cancers apart is the way we talk about their location. Typically, when you hear someone talk about cancer, they also talk about the body part where it originated: if a tumor arises from a lung cell, it's a lung cancer. If it arises from a breast cell, it's a breast cancer.

> ***Iyer:*** *Neuroendocrine cancers, it's a little bit different. These are cells that are present all over the body, in all parts of the body.*

As a result, neuroendocrine cancers can arise just about anywhere. Because of this, they are identified by the place in the body where the tumor first appeared. This is called their "primary site." So instead of having breast cancer, someone would be diagnosed with a neuroendocrine cancer with a breast primary. This tumor would share characteristics with other neuroendocrine neoplasms, not with breast cancer.

Neuroendocrine cancer isn't just one disease, however; it's a spectrum of disease.

On one end of this spectrum are neuroendocrine tumors, or NETs. These make up the majority of neuroendocrine cancers. They can be slow-growing, and can often be treated effectively for many years.

On the other end of the spectrum are neuroendocrine carcinomas. These make up less than a quarter of neuroendocrine cancers. They are characterized by very rapid growth, and tend to metastasize aggressively. Neuroendocrine

carcinomas are also much less likely to be "functional" than neuroendocrine tumors.

There are a few ways doctors can distinguish neuroendocrine carcinomas from neuroendocrine tumors. The most essential differences show up under a microscope.

When a pathologist looks closely at the cells that make up neuroendocrine tumors, they see hardly any cells in the process of dividing. This shows that it is growing slowly.

> ***Gay:*** *Whereas the tumors that are classified as neuroendocrine carcinomas are at the opposite pole. Often nearly every cell in the tumor is in an active state of division. And so it's not uncommon to look under the microscope and see virtually all the cells in the process of dividing.*

The way doctors describe the speed at which a tumor is growing is by giving it a "grade."

> ***Iyer:*** *When tumors have cells that are growing, but only up to 3% of them are growing at any given time, we tend to call these grade one or low grade, and we label them as neuroendocrine tumors.*
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> *If it's more than that, 3-20%, we call them intermediate grade, grade two. And we realize that they're slow growing, but a little bit more than the lowest grade, for example. And anything more than 20%, we call these high grade.*

Neuroendocrine carcinomas are high grade tumors.

Another key thing pathologists look at is something called a tumor's "differentiation."

> ***Gay:*** *That's a description of the organization that you see under the microscope. Does it bear any resemblance to*

what you'd expect to see there, or does it look completely disorganized? Like a, like a tumor that's, that's running rampant?

A neoplasm can be "well-differentiated" or "poorly differentiated." If the cells do not have a defined appearance, the tumor would be described as "poorly differentiated." Neuroendocrine carcinomas fall into this category.

The third thing pathologists look at is the size of the cancer cells. This helps them define a tumor as "small cell" or "large cell."

Gay: *And so small cells under the microscope have very large nuclei and otherwise very small amount of cytoplasm. So the cells themselves are quite small and almost all nucleus. Whereas a large cell has a lot of room outside of the nucleus and it makes the cell larger.*

Sometimes, a tumor can have a mix of large cells and small cells. Neuroendocrine carcinomas tend to be made of small cells.

Gay: *Large cell neuroendocrine carcinomas are relatively rarer, in most organ sites. Small cell is the dominant type that we see there.*

So, to recap: when we are talking about a neuroendocrine carcinoma, the general characteristics are that they are very aggressive, small cell, high grade, poorly differentiated tumors.

Gay: *And I think it's important to emphasize all of those different terms because patients may not be told they have a neuroendocrine carcinoma, some of these other terms may be used to describe it.*

> *Some pathologists will describe it in those terms. Some oncologists will describe it- so they may have heard that they have a poorly differentiated carcinoma, or a high grade neuroendocrine neoplasm, and all of these things, for better or worse, especially from a patient standpoint, I think are relatively synonymous.*

We mentioned earlier that neuroendocrine cancers can arise anywhere in the body. The same is true of neuroendocrine carcinomas. However, the most common location by far is the lung.

> ***Chauhan:*** *I would go on to say almost 95% of all high grade neuroendocrine carcinomas are small cell lung cancer.*

These tumors tend to arise in older adults who have a history of smoking.

The remaining 5-percent of neuroendocrine carcinomas can show up almost anywhere, in people of any age.

> ***Chauhan:*** *I've seen young and healthy people with rectal neuroendocrine carcinoma, a pediatric case with ovarian neuroendocrine carcinoma, a lot of cervix small-cell neuroendocrine carcinoma unfortunately afflicts younger female population.*

Part of what makes it difficult to determine who is at risk for neuroendocrine carcinoma is that we don't have a good understanding of what causes it. This is because research on neuroendocrine carcinoma has lagged compared to other, more common cancers.

We do know that with Merkel cell carcinoma, which is a neuroendocrine carcinoma of the skin, is associated with UV exposure and a viral infection called Merkel cell polyomavirus.

There is also an unusual scenario that sometimes occurs, where a different kind of cancer begins developing the *qualities* of neuroendocrine carcinoma.

> ***Chauhan:*** *Examples would be prostate cancer, during its evolution and exposure to various treatment, can transform into prostate high grade neuroendocrine cancer, or small cell neuroendocrine cancer of prostate. Similar transformations have also been noted in lung cancers and other cancers.*

No matter where they start and how they arise, neuroendocrine carcinomas are very aggressive. While the majority of people diagnosed with neuroendocrine *tumors* can live for many years with their disease, the same is not true for people diagnosed with neuroendocrine carcinoma.

> ***Chauhan:*** *The median survival from time of diagnosis for high grade poorly differentiated carcinomas is one to two years. And five year survival is less than 10%.*

> ***Gay:*** *It does vary a bit depending on the location from which the tumor arose because we may have more, or fewer, options for treatment on the basis of that. But unfortunately the life expectancies tend to be relatively short, especially when viewed against other neuroendocrine neoplasms.*

Deb Roberston: *I'm Deb Robertson. I live in Lombard, Illinois. My diagnosis is I have high grade neuroendocrine carcinoma, which is a very aggressive terminal cancer.*

I went in for something totally unrelated. I had a slight pain in my side, and my wife said, "You need to go to the doctor and just get it checked out." So I went to the doctor and they wanted to do a CT scan just to be safe. They did a CT scan and I got a call the next day from the doctor stating that my

liver was full of tumors. The tumors initially, they believe, began in my stomach area and then metastasized to my liver.

I was blown away. I had no other pain other than the slight pain on the side of my body. They did a biopsy and then realized that it was high grade neuroendocrine cancer. And they explained to me what that was, that there was no cure for the disease, and there was minimal medication that was effective.

I went into a little shock. I did reach out to my family, and the journey began then, and that was in January of 2022.

I immediately started chemotherapy. It worked well initially, but again stopped working. So I've gone through four types of chemotherapy. I'm currently in a clinical trial that showed some progress in stabilizing my tumors and actually shrinking them, which was wonderful, for about eight months. And then, they found tumors in my brain. That's the recent thing that's going on.

I personally am doing well, because I've been with this disease three years, which is a long time. And I'm, I'm shocked that I'm still here. You know, there's ups and downs. Sometimes it's hard. Some days I don't want to accept it. I pretend I don't have, you know, a terminal illness. You know, some days I just want to be normal.

But my relationships with my mom and friends and some family members have really flourished. And I'm very grateful for developing the closeness that we have now.

You know, knowing each other and supporting each other and being there for when you get a bad scan and you find out your cancer's spreading. And also to share in the joy of when it's stable and you're doing okay.

When someone tells you there's no cure for your disease and that you're gonna die, that's a hard pill to swallow. You

know, it's, it's hard. And you can let it consume you. Or you can do things like reach out to newly diagnosed people, and helping them through their journey, sharing your journey with them, help them understand that there can be good times in this journey. And you have to grab onto those good times and really ingest them into your life because you need that to feed you, to get through the tough times.

Earlier, we learned that cancer is caused by a mutation in a cell that causes it to multiply uncontrollably. We also learned that neuroendocrine carcinoma is an uncommon kind of cancer that typically arises from neuroendocrine cells, and is characterized by rapid growth and metastasis.

Because it grows so quickly, often just a few months go by in between the moment when a cancer begins and the diagnosis of a neuroendocrine carcinoma.

This diagnosis usually comes about because of symptoms related to the cancer's growth and spread.

> ***Gay:*** *The symptoms come about very early in this disease process. This is often something that we think, you know, arises and within three to six months, patients are overtly symptomatic, undeniably symptomatic.*

Some of these symptoms can vary depending on where the tumors are present. A lung tumor might cause shortness of breath, a persistent cough, or blood in the phlegm. Tumors in the GI tract might cause abdominal pain, or bloody stool.

Regardless of the tumor location, the cancer very quickly takes a toll on the entire body.

> ***Gay:*** *By virtue of its aggressive behavior, neuroendocrine carcinomas tend to present with sort of a consumptive illness. And so patients are often losing weight, losing*

appetite. Losing energy at a very rapid clip. So patients may say, unintentionally, I've lost 30 pounds in the last two or three months.

It is not just the primary tumor that causes these effects: since this is such an aggressive cancer, about two-thirds of patients have metastases in other organs by the time they are diagnosed.

Chauhan: *Majority of patients by the time they present symptoms, it's because the cancer has metastasized and invaded other organs and is causing them to feel sicker, be it weight loss, be it pain or other symptoms. So by far, the vast majority of patients present with advanced disease.*

Neuroendocrine carcinomas often metastasize to the same organs. These include the brain, the liver, and the bone marrow. These metastases can give rise to an *additional* set of symptoms.

Gay: *It's not unusual to see patients with neuroendocrine carcinoma of any organ site presenting with neurologic deficits because of brain metastases, or focal pain because of bone metastases.*

And these are the sorts of things that often bring patients to medical attention. Because a lot of our organs can withstand a lot before they give us signals that there's something awry, right? We can tolerate a lot of abnormality in our liver, in our GI tract, in our lungs, before we become symptomatic. That's not true in our brain, and certainly not true in our bones. Those things become symptomatic quite quickly.

If someone is experiencing these symptoms and goes to the hospital or their doctor's office, they will not immediately be diagnosed with neuroendocrine carcinoma. There is a series of tests that need to be done to determine first that it is cancer, and then to pinpoint the specific type of cancer.

The process of diagnosis usually begins with scans and imaging.

> ***Iyer:*** *We usually start with a CT scan of the chest, the abdomen, the pelvis, and try to identify its location, its size, its spread, and the amount of, you know, burden of cancer.*

If tumors show up on these scans, the next step is to do a biopsy. This is when a small sample of the tumor is removed so it can be studied.

> ***Gay:*** *So this is often done with a needle biopsy, frequently done from the outside. So the practitioners will use an ultrasound to guide a needle into a tumor site.*

This tumor sample is then sent to a pathologist, who examines it under a microscope. They look at the cells and how they are organized, which allows them to determine what type of cancer it is.

> ***Iyer:*** *And the pathologist is usually readily able to say, based on its appearance, that this is a neuroendocrine carcinoma.*

A pathologist will also use dyes or stains to see how quickly the cancer is growing.

One of the dyes pathologists often use is called Ki-67. It shows the percentage of cells that are actively multiplying. If a high proportion of cells are growing, then the tumor is high-grade.

> ***Chauhan:*** *For an example, a well-differentiated neuroendocrine tumor often tends to have lower Ki-67. But a small cell correlation neuroendocrine carcinoma would have Ki-67 of 70, 80, even 90, 95%.*

So these are all the clues that a pathologist use, different stains and their morphological architecture, to either categorize them as a well differentiated or poorly different neuroendocrine carcinoma.

At this point, a patient may be given a definitive diagnosis of high-grade, poorly differentiated neuroendocrine carcinoma.

This diagnosis is followed by *more* imaging and scans, to determine exactly how widespread the cancer is in the body. This is the "stage" of the cancer. The least advanced cancers are described as stage 1, somewhat advanced as stage 2 or 3, and very advanced as stage 4.

Chauhan: *It's very important to stage the cancer properly because if we are dealing with early stage cancer, that means stage one, two, or three, we treat with intention of cure.*

If the cancer's already spread to another organ system, and this is an advanced, or stage four cancer, we treat with an intention of prolonging a patient's life, or palliative and not curative.

The first scan patients usually get is another CT scan. For some, this might be followed up with a PET scan, and maybe an MRI of the brain.

Gay: *We want to image these patients from head to toe. Because the disease has such a high metastatic potential that we assume the disease to have spread until proven otherwise.*

At the end of this whole diagnostic process, a patient will be told some combination of the words: stage 4, high grade, poorly differentiated neuroendocrine carcinoma. At this point, those words might be almost meaningless, and all the patient hears is that they have an aggressive, incurable cancer.

This is when some people go home in a daze, get on the computer, and find the support group run by Susan Meckler-Plummer.

> ***Meckler Plummer:*** *Neuroendocrine carcinoma is just a whirlwind. You're fine one day and you have pain in your abdomen and you go to the doctor and you think, "It's an appendix, what more could it be?" And you're told you have weeks to live.*

Receiving a diagnosis of a rare, aggressive cancer can be overwhelming, confusing, and frightening. Susan says a lot of people panic.

> ***Meckler Plummer:*** *You know, it is not like getting a colon cancer diagnosis. It's not like getting a breast cancer diagnosis. This is as bad as it gets. It just is. And I think people shut down.*

It's completely normal to have a reaction like this to a serious diagnosis. At the same time, it's important to wrap your head around it as much as possible, so that you can make decisions about what comes next for treatment and care.

During her conversations with new patients in her support group, Susan will talk them through their particular diagnosis.

> ***Meckler Plummer:*** *They're going to get a lot of information about pathology. What is the cell differentiation? What is the Ki-67 from that pathology report? What do the scans show? Where are the tumors? What stage is it? Those things are very important.*

These details are essential, because they will have an impact on what treatment could look like going forward.

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With other, slow-growing neuroendocrine tumors, patients are often advised to seek out a specialist before starting treatment. This is not the case with advanced neuroendocrine carcinoma, since these tumors grow so quickly.

> ***Chauhan:*** *Please don't wait to see a specialist to get a second opinion and then make a treatment decision. This is a very different disease than well differentiated neuroendocrine tumor.*

> ***Gay:*** *This is a disease that needs immediate diagnostic workup and an immediate treatment plan. And then once that is started, I think some of this other consideration can follow, as opposed to doing it in the opposite order. Which is the way many cancer patients will approach things and is often advisable, just not in this specific circumstance.*

For patients with less advanced disease, or once initial treatment has started, it can be a good idea to seek out more specialized care.

> ***Gay:*** *I think they should be doing two things in parallel. So one is, if they're not yet established with an oncologist, someone in the oncology sphere, they should establish with whoever can see them the soonest, and most conveniently, especially if there is a significant symptom burden.*
>
> *But they should be, in parallel, seeking out major cancer centers, academic cancer centers, where clinical trials may be available and neuroendocrine carcinoma experts might be available. Those things should not be viewed as mutually exclusive.*

Some patients may worry that these more urgent interventions could exclude them from clinical trials down the line. That's true for many other cancer diagnoses, but often exceptions are made for high grade neuroendocrine carcinoma.

> ***Gay:*** *And so start something, but also begin formulating what your long-term plan is. If there's someplace that you would prefer to be seen, or a physician that you would prefer to manage your care, start working on that at the same time. Maybe you see them, you know, a few weeks later and they can handle your treatment for the remainder of the course.*

The main concern with neuroendocrine carcinoma is how aggressive it is. The goal of treatment is to slow down growth and spread as soon as possible.

A typical treatment plan often begins with chemotherapy.

> ***Iyer:*** *Usually with a doublet, meaning two different chemotherapy drugs. Often platinum is one of the drugs and etoposide another, and these are given as an outpatient IV, usually.*

Chemotherapy is initially very good at controlling the cancer, and most patients see a favorable response during treatment. But unfortunately, these results don't tend to last.

> ***Iyer:*** *Only about 15% of these are really durable responses. For the majority, this benefit is short-lived and within six months or a year, we often find that the cancer has either spread or started to grow back.*

> ***Chauhan:*** *So whenever we are starting the treatment, I almost always think ahead, what would be my plan B and plan C options?*

For small-cell lung cancer, which is a unique subset of high grade neuroendocrine cancer, adding immunotherapy has been shown to help control the disease. Immunotherapy harnesses the power of the immune system to attack a cancer.

Immunotherapy is sometimes used for tumors outside the lung, but this use is still investigational and depends on the patient and their disease.

Because there are so few options, many doctors think it is essential to include clinical trials in a patient's treatment plan, often from the very beginning.

> ***Gay:*** *I think for too long we've considered clinical trials, sort of a last resort, right? You've exhausted the available therapies and now you're going to try something experimental.*
>
> *I think, frankly, for someone with a neuroendocrine carcinoma, I think those patients should be looking for clinical trial options from the outset, from the get-go.*

While the established treatments for this disease have limited efficacy, we are in a golden age of cancer research. For patients with neuroendocrine carcinoma, there are more new treatments in the works than there have ever been before.

This includes clinical trials looking into different chemotherapies, combination therapies, and immunotherapies.

> ***Chauhan:*** *Lately there's been a lot of movement towards the betterment in finding newer targets, newer treatments. So stay tuned. This field is going to see a lot of, hopefully good, better breakthroughs.*

There is more work being done every day to discover new treatments for this disease, and NETRF is proud to support this progress.

Lori Dolnick: *My name is Lori Dolnick, and I live in New Jersey. My diagnosis is I had a stage four neuroendocrine carcinoma. So it was found initially in the bladder. And then*

they went on an Easter egg hunt, and they found it also in the liver.

So a very close friend of mine is a cancer thriver and she's been at stage four for, I think 13 or more years with her doctor. So I went to her doctor for a second opinion. I called him on a Friday after I got the diagnosis. He saw me on Monday. And he was like, "this is an aggressive cancer. You need to be treated like now, like this instant." And in 48 hours, I was getting treatment.

So I started chemo in December of '23. And I had 8 rounds of chemo, which is a lot. Because I was withstanding it and the tumors were shrinking. Then I was on immunotherapy, which didn't do anything for me, and the tumors came back.

So they put me on a targeted therapy that actually made me very sick. And because I was having such a difficult time with this other targeted therapy, he decided to put me on a new drug, which just came out in May of last year called Indeltra.

And it's a drug that's used to treat small cell lung cancer. And even though my cancer was in the bladder and liver my pathology lined up perfectly with Indeltra. So he put me on it and it literally wiped out the cancer.

So at this point, I'm eight months clear with that targeted treatment. So I just am continuing to get treated every other week. I'm still going to infusion.

It's so new. I don't know how long I'm going to be on it. I'm probably part of some paper somewhere. But I know I'm scheduled to have it for like a year.

You know, I'm just so appreciative of the fact that, when you're living with something that doesn't have a cure, that you have doctors and researchers working passionately to find those next treatments, to find those plan B's and plan C's. Because if the drug stops working, or if your body can't

tolerate it, you need that next level of drugs, the next treatment, the next thing that's going to help.

And, thank goodness for medical science. Thank goodness we live in a day and an age where all this is accessible to us. I wouldn't be walking around and be unable to work from my company of 30 years, unable to take care of my family, you know? So this is- every day is like a gift.

Whether you are a patient, a caregiver, a family member, or a friend, neuroendocrine carcinoma is a life-altering disease.

From the shock of diagnosis to the challenges of treatment, this journey is a difficult one.

But know this: there are doctors and researchers who have devoted their careers to helping people with this disease, and are making progress every day.

And there are groups, like the one Susan Meckler-Plummer runs, where patients can come together to share their experiences.

> ***Meckler Plummer:*** *The high grade neuroendocrine carcinoma group was started about seven, eight years ago, because there was nothing like that out there.*

Today, there are more than 1500 people in Susan's group, which is on Facebook. It includes people from all over the world, from the United States to Thailand and everywhere in between.

They have regular video calls to answer questions about treatments and scans, or to talk about what people are going through.

> ***Meckler Plummer:*** *This group is lifesaving. It is not your typical Facebook group. Because everybody understands exactly what they're going through.*

And I think that is the biggest takeaway, is that hearing stories from someone else, telling, sharing your story, there's nothing like that. Nothing.

Susan says that the most important thing to remember is that no matter what, you don't have to go through this alone.

CREDITS

Thanks for listening to NETWise. I'm Jessica Thomas, Director of Patient Education at NETRF. It was written and produced by Anna Van Dine; post-production by Alex Brouwer; executive producer, David Hoffman.

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Special thanks to everyone we interviewed for this episode. If you have a story to tell about your own neuroendocrine cancer journey, please email us and let us know – podcast@netrf.org

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